REMARKS

Comments regarding restriction requirement

Claims 24, 25, 29, 30, 41 and 42 are "method of making" and "method of use" claims which depend from product claim 21. Therefore, upon allowance of claim 21, it is believed that claims 24, 25, 29, 30, 41 and 42 should be rejoined and considered, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)." See also MPEP § 821.04 Rejoinder which states:

> if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claims will be rejoined.

Enablement rejection under 35 U.S.C. § 112, first paragraph

Claims 21, 22, 27, 28 and 43-45 were rejected allegedly because the "[t]he specification does not enable any person skilled in the art . . . to practice the invention commensurate in scope with these claims." In particular, the Office Action purports that an enabling disclosure has not been provided with respect to the recited biologically-active and immunogenic polypeptide fragments. This rejection is traversed.

At the outset, note that this rejection should not apply to claims 28 and 43, because the recited "fragments" of SEQ ID NO:3 and SEQ ID NO:5 are not within the scope of claims 28 and 43.

The present Specification explicitly discloses the amino acid sequences of SEQ ID NO:3 and SEQ ID NO: 5, as well as polynucleotide sequences encoding those polypeptides. Polypeptide fragments of SEQ ID NO:3 and SEQ ID NO:5 can be made by chemical synthesis (see, *e.g.*, the Specification at page 25, lines 10-14; and page 31, lines 23-28) or by recombinant methods (see, *e.g.*, the Specification at pages 25-31; and pages 57-58). An assay of apoptotic activity is provided at, for example, pages 58-59; and methods for determining immunogenic fragments of SEQ ID NO:3 and SEQ ID NO:5 are described, for example, at pages 59-60.

The Office Action has also asserted that an enabling disclosure has not been provided because there is no description of how to use the claimed polypeptide fragments as a therapeutic agent. However, as discussed at length in the response filed March 22, 2001, there are a number of other used of the polypeptides of the present invention. These uses include toxicological screening, disease diagnosis and drug discovery.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 ***requires nothing more than objective enablement.*** [emphasis added] How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Thus, there is no requirement under the law to provide "working examples" of what is claimed. Rather, one looks to whether the Specification provides a description of how to make and use what is claimed. The present Specification provides the requisite description.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited frag,emts of SEQ ID NO:3 or SEQ ID NO:5. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited fragments of SEQ ID NO:3 or SEQ ID NO:5.

For at least the above reasons, withdrawal of this rejection is requested.

Written description rejection under 35 U.S.C. § 112, first paragraph

Claims 21, 22, 27, 28and 43-45 have been rejected under the first paragraph of 35 U.S.C. §112 as allegedly being based on an inadequate written description. In particular, the Office Action has asserted that the disclosure does not provide an adequate written description of the recited polypeptide "variants." This rejection is traversed.

At the outset, note that this rejection should not apply to claims 22, 28 and 43, because the recited "variants" of SEQ ID NO:3 and SEQ ID NO:5 are not within the scope of claims 22, 28 and 43.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.* *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the claimed "variants" of SEQ ID NO:3 and SEQ ID NO:5.

The subject matter encompassed by the claims is either disclosed by the specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 21 recites a "polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5". The amino acid sequences of SEQ ID NO:3 and SEQ

ID NO:5 are explicitly disclosed in the specification. See, for example, the Sequence Listing. One of skill in the art would recognize amino acid sequences which are variants of SEQ ID NO:3 or SEQ ID NO:5. Given SEQ ID NO:3 and SEQ ID NO:5, one skilled in the art would be able to describe variants of these amino acid sequences. In this regard, see also the specification at page 4, lines 16-18; page 8, lines 16-19; and page 21, lines 8-11. Accordingly, the specification provides an adequate written description of the recited polypeptide sequences.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the language of independent claim 21 recites chemical structure to define the claimed genus:

21. An isolated polypeptide selected from the group consisting of:
a) a polypeptide comprising the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5;
b) a polypeptide comprising a naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5;
c) a biologically-active fragment of at least 30 contiguous amino acid residues of a polypeptide having the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said fragment having apoptotic activity; and
d) an immunogenic fragment of at least 30 contiguous amino acid residues of a polypeptide having the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present

claim: is defined in terms of the chemical structure of SEQ ID NO:3 and SEQ ID NO:5. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides. The polypeptides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "a large variable genus". Available evidence illustrates that, rather than being a large variable genus, the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to apoptosis associated proteins related to the amino acid sequences of SEQ ID NO:3 or SEQ ID NO:5. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as apoptosis associated proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:3 or SEQ ID NO:5. The "variant language" of the present claims recites "a polypeptide comprising a naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:3 or

SEQ ID NO:5" (note that SEQ ID NO:3 has 238 amino acid residues and that SEQ ID NO:5 has 410 amino acid residues). This variation is far less than that of all potential apoptosis associated proteins related to SEQ ID NO:3 or SEQ ID NO:5, *i.e.*, those apoptosis associated proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:3 or SEQ ID NO:5.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of May 13, 1998. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:3 and SEQ ID NO:5, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and

Fiers. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:3 and SEQ ID NO:5. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed subject matter, and withdrawal of this rejection is therefore requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 843-7352.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 3, 6, 7, 9-12, 20 and 23 have been cancelled.

Claim 21 has been amended as follows:

21. (Twice Amended) An isolated polypeptide [comprising an amino acid sequence] selected from the group consisting of:

a) [an] a polypeptide comprising the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5;

b) a polypeptide comprising a naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5;

c) a biologically-active fragment of [the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5 comprising] at least 30 contiguous amino acid residues [and] of a polypeptide having the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, said fragment having apoptotic activity; and

b) an immunogenic fragment of [the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5 comprising] at least 30 contiguous amino acid residues of a polypeptide having the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5.